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THE AMYLOIDOSES: CLINICAL FEATURES, DIAGNOSIS AND TREATMENT

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Abstract

Amyloidosis is a rare disorder in which insoluble amyloid proteins are deposited in body organs, causing abnormal protein build-up in tissues and eventually leading to organ dysfunction and death. It affects less than 200,000 people in the United States, classifying it as a rare disease according to the National Institutes of Health. Definitive determination of the underlying protein is critical since prognosis and treatment of amyloidosis can vary widely depending on the responsible protein. The following paper describes the various types and clinical features of amyloidosis and provides an overview of current diagnostic tools and therapies.

Introduction

The amyloidoses are disorders of protein conformation and metabolism in which insoluble fibrils are deposited in body organs, causing organ dysfunction and eventually death. Approximately 60 heterogeneous amyloidogenic proteins have been identified, 27 of these associated with known human disease.[1] The unifying feature of these proteins is their tendency to form β-pleated sheets aligned in an antiparallel fashion. These sheets then form rigid, nonbranching fibrils that resist proteolysis and cause mechanical disruption and local oxidative stress in affected organs such as the heart, liver, kidneys, and gastrointestinal tract.[2] Table 1 lists the most commonly seen forms of systemic amyloidosis, the protein responsible, and the organs in which amyloid deposition commonly occurs.

The word "amylon" was first used in 1834 by the German botanist Matthias Schleiden to describe the waxy starch in plants. Rudolph Virchow then coined the word "amyloid" in 1854 to describe tissue deposits that stained like cellulose when exposed to iodine. Pathologists now know that amyloid, using the Congo red stain introduced in the 1920s, looks pink with normal lighting and demonstrates apple-green birefringence under polarized light.[3] The various types of amyloid are indistinguishable using light microscopy. It is therefore essential for the pathologist to perform additional studies to definitively identify the type of protein involved, since the prognosis and treatment of amyloidosis can vary widely depending on the protein responsible.[4, 5] Amyloid can be speciated using light microscopy or immunogold electron microscopy after reacting the specimen with specific antiserum. Alternatively, protein separation and identification can be performed using mass spectrometry.[6]

Case Number 1

A 48-year-old woman with no significant past medical history presented to the hospital with anasarca and was found to have nephrotic range proteinuria. Kidney biopsy demonstrated amyloidosis involving the blood vessels, interstitium, and

Type of Amyloidosis	Responsible Protein	Organs Affected
Primary (AL)	Monoclonal light chains	Heart, kidneys, liver, peripheral and autonomic nervous system, GI tract
Senile systemic (ATTR)	Wild-type transthyretin	Heart
Hereditary (ATTR)	Mutant transthyretin	Heart
Hereditary (AApoA1)	Apolipoprotein 1	Heart, kidneys, liver, peripheral nervous system, skin
Hereditary (AFib)	Mutant fibrinogen A alpha	Kidneys, liver
Hereditary (ALys)	Lysozyme	Kidneys, liver
Isolated atrial (AANF)	Atrial natriuretic factor	Heart
Secondary (AA)	Serum amyloid A	Kidneys, GI tract, heart
Dialysis-related ($A\beta_2M$)	β2-microglobulin	Osteoarticular tissue, GI tract, circulatory system
Finnish-type (AGel)	Gelsolin	Lattice dystrophy of cornea, corneal neuropathy

Table 1. Common forms of systemic amyloidosis.

glomeruli. Bone-marrow biopsy revealed clonal plasma cells accounting for 23% of the marrow cellularity. Diagnoses of systemic primary (AL) amyloidosis and smoldering multiple myeloma were made. Echocardiography was remarkable for moderate concentric left ventricular hypertrophy with a thickened interventricular septum, dilated atria, a plethoric inferior vena cava, and a pulmonary artery pressure (PAP) of 67-70 mm Hg. After 2 years of treatment with thalidomide and dexamethasone, her PAP normalized and her interventricular septum diameter approached normal; nonetheless, autologous peripheral blood stem-cell transplantation was complicated by atrial fibrillation, hypotension, and volume overload. She remains in hematologic remission without evidence of progressive organ dysfunction while taking maintenance lenalidomide.

Primary (AL) Amyloidosis

The most common type of amyloidosis results when light chains are produced in excess by clonal or frankly malignant plasma cells. It occurs in 10-15% of patients with full-blown multiple myeloma but can also be seen when the affected patient has less than 10% bone marrow plasma cells, the quantity typically required to make a diagnosis of myeloma. Light-chain amyloidosis may also arise in association with non-Hodgkin's lymphoma and Waldenström's macroglobulinemia.[7] It is a relatively rare disease with an incidence of 5.1-12.8 per million person-years and only 1,275-3,200 new cases being diagnosed in the United States annually.[8] The male-to-female ratio is 3:2. Although healthy individuals have a preponderance of kappa free light chains (K/λ = 2:1), the reverse is true in most patients with primary amyloidosis, as excess lambda light chains have a greater propensity to be amyloidogenic.[9]

Presentation

Close to 90% of patients will have profound fatigue, weight loss, and edema. Edema may have multiple causes, including hypoalbuminemia (from kidney, bowel, or liver involvement), right-heart failure, or simply the impairment of the blood vessels' ability to handle hydrostatic pressure challenges. Other presenting symptoms depend on the organs most prominently involved in a given patient. Liver involvement is seen in 15-25% of patients, neuropathy in 15-20%, and cardiac involvement in up to 50%.[9] Symptomatic heart failure, seen in 25-33% of patients, portends a median survival of less than 6 months.[10] Renal involvement manifests as nephrotic syndrome. Involvement of the gastrointestinal tract causes macroglossia, diarrhea due to malabsorption, gastric hypomotility, and constipation. In 30% of patients, three or more organs are involved.[7] Amyloidosis may also cause orthostatic hypotension, hypothyroidism, reticulonodular infiltrates and amyloidomas in the lungs, pleural effusions, nodular deposits in the skin, lymphadenopathy, and splenomegaly. Periorbital purpura and other manifestations of a bleeding dyscrasia arise as a result of vascular infiltration by amyloid, production of a dysfunctional fibrinogen molecule by the amyloid-impaired liver (dysfibrinogenemia), abnormal platelet aggregation, and deficiencies of factors II, V, VII, IX, and particularly X.[11] Factor X has a predilection to bind to amyloid fibrils, and its resultant deficiency cannot easily be corrected by administering plasma because the infused factor X rapidly binds to large amyloid deposits in the liver and spleen without causing a concomitant rise in the blood's factor X level.[12]

Diagnosis

The diagnosis of AL amyloidosis can be made in several ways, although the first critical step is clinical suspicion. Serum protein electrophoresis with immunofixation electrophoresis (SPEP/IFE) is a frequently used screening test that can be deceptively normal in 25% of those with amyloidosis because either the pathogenic light chains are produced in small amounts or they are fully and completely filtered by the kidneys and therefore not present in quantities large enough to be detectable in the serum. When used in combination with SPEP/IFE, a 24-hour urine collection with urine protein electrophoresis and IFE can detect 90% of those affected by amyloidosis. A recent addition to the diagnostic armamentarium is the serum free light chain assay, which quantifies the amount and type of even very small amounts of free light chains; this is abnormal in 99% of those with AL amyloidosis.[13] Even with abnormalities of these protein studies, tissue biopsy confirmation of the diagnosis is required. The sensitivity of abdominal fat pad aspiration is around 85%,[14] rectal biopsy is 75-85%, and bone marrow biopsy about 50%.[15] If suspicion is high and the preceding tests are not definitive, biopsy of the affected organs can be considered, but the risks need to be weighed carefully in light of the tendency of amyloidosis patients to suffer hemorrhagic complications. It is usually best to proceed with the least invasive procedures first.

Treatment

The treatment of AL amyloidosis has evolved rapidly in recent years, mirroring changes in the treatment of multiple myeloma. In 1978, Robert Kyle reported a double-blind, randomized, placebo-controlled trial assessing the efficacy of melphalan plus prednisone (the therapy of choice at that time for myeloma) in the treatment of amyloidosis. He found that one-half of the patients treated with melphalan and prednisone improved and one-quarter remained stable, but overall survival did not improve.[16] Studies since then find that overall response rates to melphalan plus prednisone are about 30% and occur slowly. The median survival averages 12-17 months but is prolonged in responding patients, where 78% will remain alive at 5 years.[17, 18] Pulse dexamethasone alone achieves overall response rates of 45% (24% complete response), while melphalan plus dexamethasone achieves overall response rates of 51-68%. The median survival with dexamethasone alone is 31 months, while it is 70 months with melphalan plus dexamethasone unless the patient has severe cardiac amyloidosis, in which case survival drops to about 24 months.[19, 20] It is important to appreciate that hematologic response (substantial diminution or obliteration of paraprotein production) only translates into organ response (improved indices of organ function) about half the time and at a slower rate.

In the last few years, immunomodulatory drugs (IMiD) like thalidomide and lenalidomide and the proteasome inhibitor bortezomib have dramatically changed the scope of treatment for multiple myeloma, and they are increasingly applied to amyloidosis. Thalidomide, the first IMiD used clinically, plus dexamethasone gives overall response rates of 48% and complete response rates of 19%, and the time to response is remarkably short at 3.6 months.[21] Care must be given to selecting the appropriate patient to receive these drugs, however, since thalidomide is notorious for causing neuropathy and constipation, symptoms that can trouble amyloidosis patients even before therapy. Lenalidomide, the second IMiD available, plus dexamethasone

gives overall response rates of 41-67% with complete response rates of 29%. The time to hematologic response is 6.2 months, and organ response may occur at a median of 9.4 months.[22, 23] Lenalidomide is less likely to cause neuropathy but can provoke fluid retention and causes significant myelosuppression in more than half the patients. Both thalidomide and lenalidomide can provoke thromboembolic events, so aspirin prophylaxis is required at a minimum. Bortezomib alone gives overall response rates of 50%, with complete response rates of 20% and an even shorter time to hematologic response of 1.2 months.[24] Even better responses can be possible with the addition of dexamethasone to bortezomib, with overall response rates of 54-80% and complete response rates of 15-31%.[25-27]

In those judged eligible, the most effective treatment for amyloidosis may be autologous hematopoietic stem cell transplantation whether or not prior chemotherapy is administered.[28] Based on early experience, patients with severe organ dysfunction have been excluded as candidates, particularly those with cardiac disease. This is discussed in more detail in the accompanying article by Dr. Kamble (see page 17).

Adjunctive therapy of amyloidosis consists of salt restriction and the judicious use of diuretics. Because cardiac function in amyloidosis is often preload dependent, it is important to avoid excessive reduction of the patient's intravascular volume. Calcium channel blockers can cause clinical deterioration due to their negative inotropic effect, and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are often poorly tolerated due to their tendency to cause hypotension. Digoxin should also be used cautiously since it can bind to amyloid fibrils and cause local digitalis toxicity even in the setting of "therapeutic serum digoxin levels." Thoracentesis or pleurodesis can be used as necessary for relief from symptomatic pleural effusions. Orthostatic hypotension can be one of the most disabling symptoms endured by patients and is best managed by wearing waist-high compression stockings and taking midodrine. Fludrocortisone is a less desirable option due to its tendency to cause fluid retention. Patients should avoid straining at micturition and defecation due to the risk of vasovagal syncope.[29] Investigational therapies include the use of R-1-[6-[R-2-carboxy-pyrrolidin-1-yl]-6-oxohexanoyl] pyrrolidine-2-carboxylic acid (CPHPC) and eprodisate. CPHPC is a palindromic compound that binds and cross-links circulating serum amyloid P component, depleting the pool available to bind amyloid and rendering amyloid deposits less resistant to proteolysis.[30] Eprodisate interferes with the interaction between amyloid and glycosaminoglycans, inhibiting the polymerization of fibrils and their deposition into tissues.[31]

Hereditary (ATTR) Amyloidosis

There are several types of hereditary amyloidosis, but the most common is ATTR amyloidosis in which aberrant transthyretin (TTR) protein deposits cause severe peripheral and autonomic neuropathy, and sometimes cardiac or renal disease, leading to death within 5-15 years of symptom onset. More than 80 different mutations in transthyretin, a carrier protein for albumin, have been described. They are inherited in an autosomal dominant fashion and typically cause amino acid substitutions that allow dissociation of the normal transthyretin tetramers followed by their accumulation in the nervous system and heart. Typical signs and symptoms include hyperesthesia to pain and temperature, motor weakness, impotence, decreased bowel motility, diarrhea, weight loss, incontinence, orthostatic hypotension, vitreous opacities, and diminished deep-tendon reflexes.[32] Liver transplantation, which removes the source of variant TTR production, can arrest the progression of peripheral and autonomic neuropathy[33] but is only effective if used relatively early in the disease's course, before significant gastrointestinal disease has developed. Interestingly, it does not seem to improve cardiomyopathy.[34] Diflunisal, a nonsteroidal anti-inflammatory drug that attaches to the thyroxine-binding site of the TTR tetramer, can stabilize the protein and counteract its tendency to develop a beta-pleated sheet conformation.[35]

Case Number 2

A 50-year-old female with chronic anemia complained of a 3-month history of dyspnea on exertion. One month prior to presentation, while taking oral contraceptives, she had suffered a deep venous thrombosis of her leg that necessitated thrombectomy. Her physical examination was notable for obesity, 2+ bilateral lower extremity edema, and scarring related to her recent procedure. Her serum chemistry results were within normal limits, but she had nephrotic-range proteinuria, losing 4,761 mg of protein in her urine every 24 hours. No pulmonary emboli were found on ventilation and perfusion scanning. Echocardiography was remarkable for severe concentric left ventricular hypertrophy, a diminished ejection fraction of 45-50%, a pulmonary artery pressure of 50-55 mm Hg, and a dilated inferior vena cava. Serum protein electrophoresis, urine protein electrophoresis, serum free light chain assay, bone marrow aspiration and biopsy, and a fat pad aspirate failed to demonstrate the presence of light chain amyloidosis. Renal biopsy revealed deposition of AA amyloid within the glomeruli and blood vessels. A large hepatic adenoma, thought to be due to her use of hormonal contraception, was found on MRI of the abdomen. Following transcatheter ablation of this tumor, her cardiac function and nephrotic syndrome improved gradually over the course of 1.5 years. She died unexpectedly after placement of a pacemaker 2 years following her initial diagnosis.

Secondary (Reactive AA) Amyloidosis

Secondary or AA amyloidosis occurs when serum amyloid A protein — an acute phase reactant produced in response to a variety of infectious, inflammatory, or neoplastic insults — accumulates in the kidneys, gastrointestinal tract, and heart. It has been associated with conditions as diverse as familial Mediterranean fever, rheumatoid arthritis, ankylosing spondylitis, severe gout, tuberculosis, bronchiectasis, osteomyelitis, inflammatory bowel disease, Hodgkin's disease, and renal-cell carcinoma. Treatment is directed at the underlying disease process.[36]

Hemodialysis-Associated ($A\beta_2M$) Amyloidosis

Hemodialysis-associated amyloidosis is due to the accumulation of beta-2 microglobulin, a component of major histocompatibility complex (MHC) class I molecules. The most common symptom is joint pain and dysfunction, but it can also involve the gastrointestinal tract and myocardium, pericardium, and cardiac valves. The only effective treatment is renal transplantation.[37]

Conclusion

Amyloidosis is a relatively rare condition caused by the accumulation of diverse normal and abnormal proteins in various bodily tissues. Effective therapy cannot be instituted unless the type of amyloid is correctly identified. Treatment of these

complicated patients requires careful coordination among a wide variety of subspecialists. This has become much more important as effective interventions have emerged for those with AL and other types of amyloidosis, and the success of therapeutic intervention is predicated on the earliest possible diagnosis.

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